REMARKS

The claims in issue are 1-3, 7-17 and 21-31. Claims 1-3 and 7-17 are original claims albeit amended as discussed, below. Claims 21-31 are new claims.

The Examiner has acknowledged applicants' election of a species from claims 3-7, 9, 13 and 15 for further prosecution and identification of all claims readable thereon. In response to said requirement to select a species, applicants selected tazarotene as the prodrug and tazarotenic acid as the drug. Tazarotene is an ester of tazarotenic acid. Original claims 3 and 7-9 read on this species. New claims 21-25 read on this species.

Original claims 1-20 have now been amended to claim, as a first embodiment of the invention, a method of sustained-delivery of an active drug to a posterior part of an eye of a mammal to treat a disease or condition affecting said mammal, wherein said disease or condition can be treated by the action of said active drug upon said posterior part of the eye, comprising administering an effective amount of an ester prodrug of the active drug subconjunctivally or perioculary, and wherein **the active drug is a retinoid** and is more than about 10 times as active as the prodrug. (See claim 1.) Thus, claims 1 and 17 were limited to retinoids. Claim 6 was cancelled as being redundant. In addition, the original claims which included active drugs other than retinoids were cancelled without prejudice, i.e. original claims 7,8 and 18-20 were cancelled.

All of the claims were rejected under 35 USC 103(a) over Campochiaro et al., Allergan Annual Report (2001), Wilkins J. (Allergan, Inc. Avage (tazarotene) Cream(2002)) and Castelhano et al. in view of Yevey et al and Chang.

(The Allergan Annual Report (2001), is hereinafter referred to as "Annual Report".

Wilkins J. (Allergan, Inc. Avage (tazarotene) Cream(2002)) is hereinafter referred to as "Wilkins".)

The Examiner argues that it would be "prima facie obvious to the skilled artisan at the time of the invention to at once incorporate and/or combine together the teachings and methods of Campochiaro, Allergan, Wilkins, Castelhano and Chang."

Campochiaro teaches that retinoids may be delivered by subconjunctival injection.

The Annual Report discloses that tazarotene may be used to treat vitreal retinopathy. (The Examiner incorrectly identifies Oculex as a tazarotene –containing product. Oculex refers to the delivery system and is not the name of the product. For example, on page 23, Ocuflox is stated to include ofloxacin as the active ingredient.)

Wilkins teaches the pharmacokinetics of the formation of tazarotenic acid from a tazarotene-containing topical cream. (Note that this reference clearly states that the product is not to be used for ophthalmic indications.)

Castelhano teaches the periocular injection of a prodrug that is converted to an active compound, in-vivo, by esterification.

Yevey et al. teaches controlled release systems using biocompatible polymers, wherein said system is a liquid formulation.

Finally, Chang teaches pharmaceutically-active compounds bound to ion exchange resins surrounded by a bioerodible polymer.

Thus, the Examiner has found 5 separate and unrelated references that he has combined to make out a prima facie case of obviousness. But the directions for making this combination is only found in the applicants' specification and not in the references. Therefore, it is believed that the Examiner has not met his burden of providing a prime facie case for obviousness. For example, since Examiner requires all 5 references to provide a case of prima facie obviousness, how is this case made when the Wilkin's specifically states that the tazarotene-containing product, Avage, can not be used in ophthalmic applications. Doesn't this statement, in and of itself, break the chain of references as they suggest the invention defined by the pending claims?

In addition, to provide the suggestion of converting the prodrug to an active by ester hydrolysis, the Examiner cites a reference, i.e. Castelhano, which teaches the ester catalyzed hydrolysis of a water-soluble deazapurine to the active drug, i.e. an A3-selective adenosine, in-vivo, wherein the applicants' discovery, as defined in amended claims 1-3 and 7-17, is that a water-insoluble retinoid may be administered as a prodrug that is hydrolyzed to an active water-insoluble retinoid. There is no

suggestion that the retinoids claimed herein may be substituted for the water soluble adenosine of the reference.

Assuming that Examiner has made a case of prima facie obviousness for the invention of claims 1-3 and 7-17, as originally filed, the applicants wish to point out that the amendments made herein overcome the rejection for obviousness.

Applicants also point to the separate patentability of the invention defined in new claims 21-31. The invention of claims 21-25 is described in Example 4, wherein it is demonstrated that subconjunctively injecting tazarotene into the eye unexpectedly provides a method of administration whereby the conversion of the tazarotene prodrug to the active drug, i.e. tazarotenic acid, is surprisingly increased. This result is not suggested by any of the references, alone, or in any combination thereof.

Example 4 is also representative and supports the broader invention which is defined in new claims 26 -31. That is, the invention of claim 26 is defined as a method of lowering the ratio of an ester prodrug to active drug in the eye as compared to when the prodrug is administered intraocularly or directly into the vitreous which comprises subconjunctival or periocular administering said ester prodrug into the eye. Support for this claim is found at Paragraph 0009 of the Published Patent Application 2005/0009910 wherein it is stated:

> "We have surprisingly discovered that an active drug can actually be delivered to the vitreous and other posterior parts of the eye by subconjunctival or periocular administration of an ester prodrug more efficiently than by direct intraocular administration of the ester prodrug. In other words, when a prodrug is administered subconjunctivally or periocularly, the ratio of the prodrug to active drug is significantly lower in the eye than it is when the prodrug is administered intraocularly or directly into the vitreous. As a result, sustained delivery of therapeutically-effective concentrations of the active drug to the posterior parts of the eye can be achieved with fewer side effects such as cataracts, and a lower risk of toxicity associated with the prodrug, by subconjunctival or periocular administration of the prodrug instead of direct intraocular or intravitreal administration of the prodrug. As such, this invention

dramatically improves the pharmacotherapy of compounds with low therapeutic indices directed at the posterior ocular structures."

It is believed that this paragraph describes the unexpected discovery that the applicants are now claiming.

If the Examiner wishes to discuss this response, he is invited to call the attorney of record at the telephone number given below.

The Commissioner is hereby authorized to charge any fees associated with this communication or credit any overpayment to Deposit Account No. 01-0885.

Respectfully submitted,

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